POPULATION CEFAZOLIN PHARMACOKINETICS BEFORE, DURING AND AFTER CARDIOPULMONARY BYPASS IN CHILDREN UNDERGOING CARDIAC SURGERY

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Background

Scarce data are available to guide cefazolin dosing in children undergoing cardiac surgery with cardiopulmonary bypass (CPB).

Objectives

The objective of this trial is to derive a model-based dosing regimen for cefazolin in this patient population.

Methods

- 56 infants and children were included and received following intravenous dosing regimen: 25 mg/kg as a bolus 30 minutes before surgical incision, just before cessation of CPB, 8 hours after the 2nd dose and 8 hours after the 3rd dose.
- Blood samples were collected before, during and after cardiopulmonary bypass. Total (n=497) and unbound cefazolin concentrations (n=494) were measured using a validated High-Pressure Liquid Chromatography method; unbound concentrations were separated using a validated ultrafiltration method.
- NONMEM® version 7.2 was used for population PK modeling and covariate analysis: one, two and three compartmental models with first-order elimination were evaluated. R®, PsN® and Xpose® tools were used for data manipulation, graphical and statistical summaries.
- Glomerular Filtration Rates (eGFR) pre-, on- and post-CPB were estimated using the Modified Schwartz formula.
- Internal validation of the final model was performed using a non-parametric bootstrap (n=500 samples), a prediction corrected Visual Predictive Check (pcVPC) (n=1000 simulations) and the Normalised Prediction Distribution Error method (NPDE)(n=1000 simulations).
- To evaluate the current dosing regimen, Monte Carlo simulations (n=1000 simulations) were performed for a typical patient, procedure duration and median eGFR during the pre-, on- and post-CPB period. A minimum time frame of 60% of the dosing interval in which the unbound drug concentration remained above the Minimal Inhibitory Concentration (MIC) of *Staphylococcus aureus* (8 mg/L) was aimed for.

Intermediate results

PATIENT CHARACTERISTIC	MEDIAN (RANGE)
Age (days)	270 (5-5439)
Weight (kg)	6.8 (2.7-70)
Procedure duration (h)	2.15 (1.21-8.50)
CPB duration (h)	1.30 (0.37-5.1)
eGFR (mL/min/1.73 m2) pre CPB	108 (32-187)
eGFR (mL/min/1.73 m2) during CPB	80 (29-112)
eGFR (mL/min/1.73 m2) post CPB	74 (27-135)
Cardiac output (L/h) during CPB	44.82 (18.36-249)
Albumin (g/dL)	36 (21.8 -53)
Priming volume (mL)	175 (150-1000)

Table 1. Patient characteristics

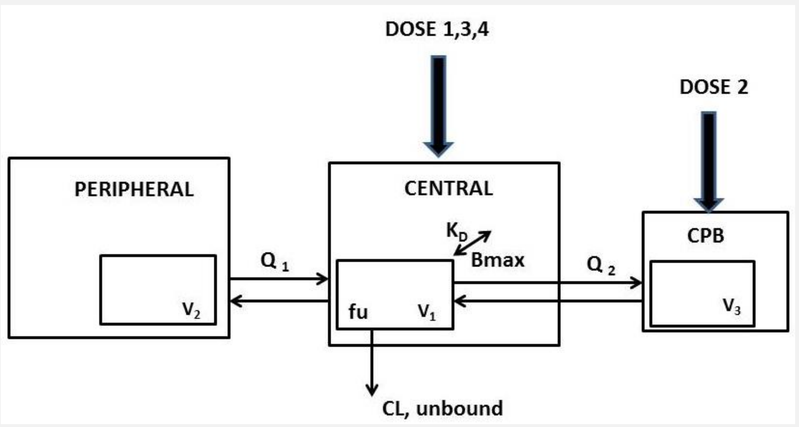

Figure 1 : Structure of the final model

Parameter	Estimate	RSE (%)	Median Estimate from Bootstrap (n=500[1])	2.5th Percentile from Bootstrap (n=500[1])	97.5th Percentile from Bootstrap (n=500[1])
Fixed effects					
$CL_{i,unbound} = CL_{pop} \times \left(\frac{WT}{WT_{med}}\right)^{0.75} \times \left(\frac{eGFR}{6.48}\right)$					
CL (L/h)	1.8	5	1.81	1.64	1.97
$Q_{i,unbound} = Q_{pop} \times \left(\frac{WT}{WT_{median}}\right)^{0.75}$					
Q1 (L/h)	4.79	6	4.84	4.24	5.45
Q2 (L/h)	FIXED to cardiac output during CPB				
$V_{i,unbound} = V_{pop} \times \left(\frac{WT}{WT_{median}}\right)^{1}$					
V1 (L)	1.87	6	1.88	1.63	2.10
V2 (L)	2.29	7	2.32	2.02	2.64
V3 (L)	FIXED to CPB priming solution volume				
$B_{max} = (\theta_{intercept} + \theta_{slope} \times albumin\ concentration)$					
$\theta_{intercept}$ (mg/L)	132	13	133	98	169
θ_{slope}	1.60	21	1.64	1.11	2.20
K_D (mg/L)	47.7	10	48.5	40.3	59.2
Interindividual variability					
ω^2 CL	0.095	28	0.088	0.046	0.15
ω^2 V1	0.111	38	0.107	0.039	0.188
ω^2 V2	0.241	25	0.232	0.116	0.365
ω^2 Bmax	0.043	38	0.040	0.016	0.074
Residual variability (proportional)					
σ^2 (unbound concentration)	0.074	11	0.073	0.056	0.091
σ^2 (total concentration)	0.026	16	0.025	0.017	0.034

Table 2. Parameter estimates ([1] 273 successful runs)

Figure 4. Prediction-corrected Visual Predictive Check (n=1000) (left: panel unbound; right panel: total concentrations)

Legend: dots: observations; solid red line: observed median; dashed red lines: observed 5th and 95th percentiles; shaded areas : 95% CI of simulated 5th, 50th and 95th percentiles

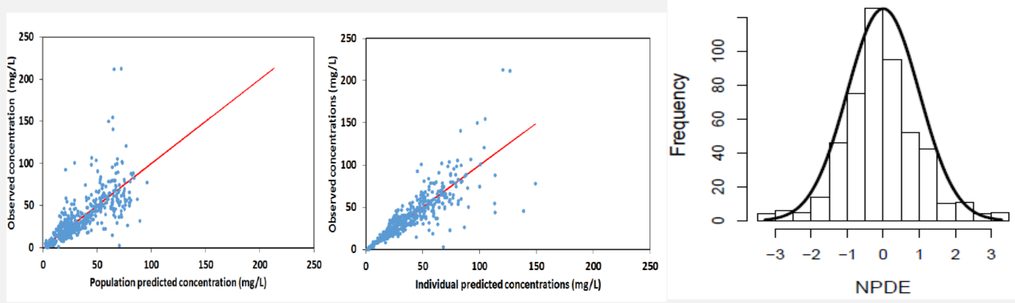

Figure 2 : Goodness-of-fit plots and distribution histogram of NPDE for unbound concentrations

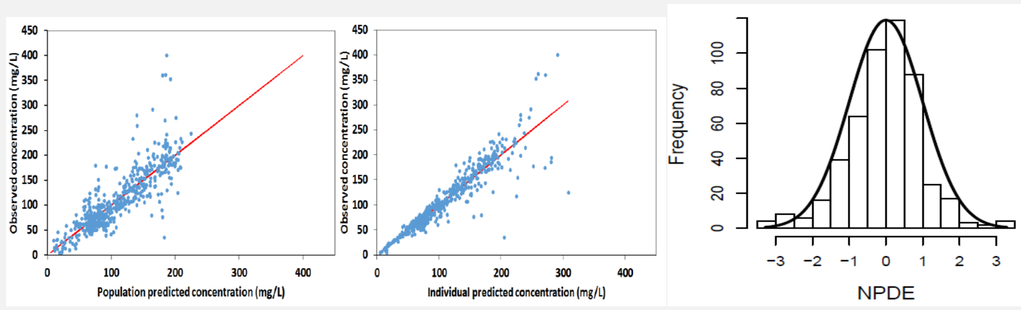

Figure 3: Goodness-of-fit plots and distribution histogram of NPDE for total concentrations

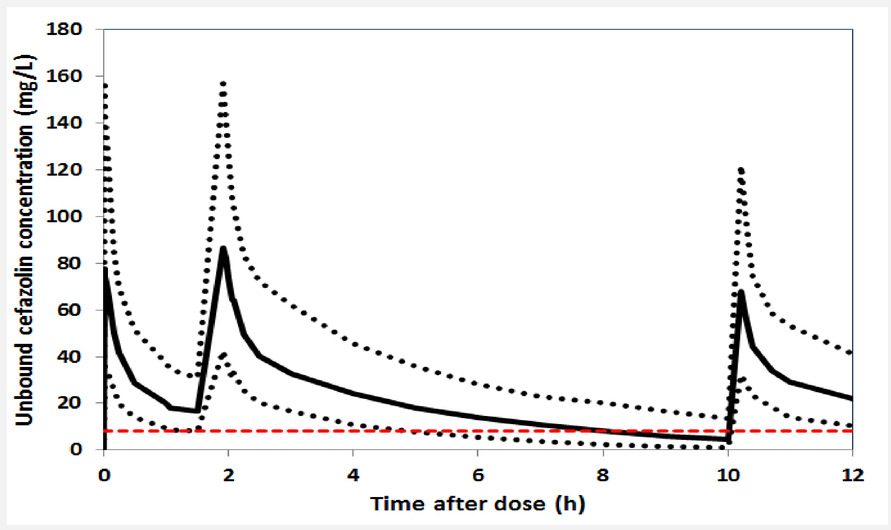

Figure 5. Monte Carlo simulations for a typical patient, procedure duration and median eGFR pre-,on- and post CPB

Legend : solid line: median ; dotted lines : 5th and 95th percentiles (n= 1000); red dashed line: MIC cut-off

Discussion and Perspectives

- The proposed model adequately describes bound and unbound plasma cefazolin pharmacokinetics in infants and children undergoing cardiac surgery with cardiopulmonary bypass.
- Based on Monte Carlo simulations, the current dosing regimen needs to be optimised with a maximum dosing interval of 5-6h in postoperative patients.
- In a next step, a tissue concentration pharmacokinetic model will be developed to investigate the adequacy of dosing in terms of tissue penetration.

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